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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/517,466	03/02/2000	James L. Hartley	IVGN 223	4289

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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/517,466	HARTLEY ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-56* is/are pending in the application.

4a) Of the above claim(s) *50-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0506*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This action is responsive to the Amendment and Reply including a complying complete set of claims filed December 21, 2006. Claims 39 and 49 have been amended. Claims 50-56, as well as claims 39-49 to the extent that they are drawn to sequences (b)-(f) of claim 39, remain withdrawn from consideration. Accordingly, claims 39-49, to the extent that the claims are drawn to sequence (a) of claim 39, remain under consideration. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and/or objections not reiterated in this action have been withdrawn. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

3. It is noted that the examiner considered document AS213 of the Information Disclosure Statement of January 21, 2005, as indicated by the examiner's initials next to that citation (see copy of Form PTO-1449 provided with the Office action of November 18, 2005).

4. With regard to the "Tenth Supplemental" IDS filed May 18, 2006, it is noted that the citation for document AR229 has not been initialed because the number of this unpublished application will not be printed on the face of an issued patent. However, the examiner reviewed the application file on March 18, 2007. With regard to

documents AS228 and AT228, the examiner has inserted the corresponding publication numbers and added the date of review to the citations provided by applicant.

Claim Rejections - 35 USC § 112

5. Claims 39-49 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated nucleic acid molecules comprising SEQ ID NO: 87 (including the molecule disclosed by applicant as SEQ ID NO: 60), does not reasonably provide enablement for any isolated nucleic acid molecule comprising the nucleotide sequence of (a) of claim 39 "located within a recombination site," for the reasons stated in the Office action of November 18, 2005, which reasons are reiterated below. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. It is also noted that **while claim 39 has been amended** to further limit the "recombination site" to a site "recognized by the integrase recombination protein," this amendment is not sufficient to overcome the rejection, for reasons discussed below in the response to applicant's arguments.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make

or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

The claims are to drawn isolated nucleic acid molecules comprising the nucleotide sequence ATTATAC located "within a recombination site" (see claim 39), as well as various vectors and host cells comprising the nucleic acid molecule. It is noted that the specification states that recombination sites "are discrete sections or segments of DNA on the participating nucleic acid molecules that are recognized and bound by the recombination proteins (p. 5)/a site-specific recombination protein (p. 33) during the initial stages of integration or recombination" (see pages 5 and 33 of the specification). Thus, the term "recombination site" as used in the specification is consistent with the art-recognized meaning of this terminology, and encompasses any sequence recognized and bound by recombination proteins during integration and/or recombination. Accordingly, the instant claims are sufficiently broad so as to encompass molecules comprising the sequence ATTATAC located within any type of recombination site.

It is unpredictable as to whether one of skill in the art could make and use applicant's invention in a manner reasonably commensurate with the claims. The specification provides evidence that the mutation of the first nucleotide of the 7 base pair overlap of the attL recombination site 15 base pair core region from T to A (such that the 7 base pair sequence changes from TTTATAC to ATTATAC) results in increased recombination efficiency (see Examples 21 and 22, and SEQ ID Nos 60 and 87 in particular). Accordingly, one of skill in the art could clearly prepare nucleic acids

comprising such mutated attL sequences and use said nucleic acids in various methods requiring site-specific recombination. However, the specification is silent with regard to other att recombination sites comprising this particular mutated sequence, and with regard to what effect this mutation would have (if any) on recombination using such sequences. Further, the specification does not disclose the use of molecules comprising this 7 base pair sequence located in any type of non-att recombination site/sequence. Thus, while the specification enables the use of one particular type of nucleic acid molecule encompassed by the claims, the vast majority of molecules encompassed by the instant claims are neither not enabled by the teachings of applicant's specification. Given the high level of skill of one skilled in the relevant art, it is clearly within the ability of such a practitioner to synthesize a variety of molecules encompassed by the claims and to, e.g., assay those molecules to determine whether any of them are useful in recombination. However, the outcome of such experimentation cannot be predicted, and therefore it is completely unpredictable as to whether such additional molecules could be successfully used in a manner analogous to the particular attL mutant sequence employed by applicant. Lacking guidance from the specification, one skilled in the art may look to the teachings of the prior art for further guidance and enablement of a claimed invention. However, in the instant case, the prior art does not disclose other molecules meeting the requirements of the claims. The closest prior art reference, Zucman-Rossi et al (Proc. Natl. Acad. Sci. USA 95:11786-11791 [9/1998]) discloses a sequence comprising a breakpoint region (EWSR1) that includes the sequence ATTATAC (see entire reference, particular page

11786 and Figure 1, as well as the sequence disclosed in GenBank Accession No. Y08806, in which ATTATAC is located, e.g., within intron 8 at nucleotide 38969). However, the sequence ATTATAC in the molecule of Zucman-Rossi et al is not located within a "recombination site" as required by the instant claims – the site flanking ATTATAC in the molecule does not correspond to that of a known recombination site, and Zucman-Rossi et al do not disclose that this particular site is a breakpoint or that recombination proteins bind this site, etc. Accordingly, the teachings of the prior art cannot be relied upon for enablement of additional molecules encompassed by applicant's claims. Thus, given the lack of sufficient guidance provided by the specification and the prior art, it would require undue experimentation to make and use applicant's invention in a manner reasonably commensurate with the instant claims.

The reply traverses the rejection on the following grounds. The response notes that the claims have been amended to recite the limitation "recognized by the integrase recombination protein." The response argues that the specification "provides sufficient guidance as to which recombination sites are recognized by the integrase recombination protein," referring to page 5, lines 15-17, and page 33, lines 26-28, and further urges that the specification "provides sufficient guidance to allow those of ordinary skill in the art to make and use" the claimed molecules.

These arguments have been thoroughly considered but are not persuasive. The specification discloses at pages 2-3 that integrase is not in fact a single, specific protein, but rather a "family of recombinases" that includes many members (citing as examples the bacteriophage λ att system, the Cre/loxP system, and the FLP/FRT system), and

further that different integrases recognize different, specific recombination site sequences. As was indicated in the Office action of November 18, 2005, the specification only exemplifies the successful use of the mutated ATTATAC sequence within the attL recombination site core region, and it is further noted that only a particular type of Clonase mix (and thus, a particular type of integrase mix) was employed in the examples provided by applicants (applicant is again referred to Examples 21-22). The specification further discloses at, e.g., page 43, that particular types of Clonase mixes are employed in different types of att site recombination reactions. Thus, based on the teachings of the specification itself, one of skill in the art would recognize that there are many types of integrases, and that particular integrases recognize different, specific recombination site sequences. It is completely unpredictable as to whether the particular, synthetic sequence recited in the claims would function successfully when placed within a different recombination site, and the teachings of the specification itself suggest that it would not, given that even different att sites function with different Clonase mixes. Further, while experimentation could be conducted so as to determine whether the sequence ATTATAC might function within the context of different core sequences, using different types of integrases, etc., the outcome of such experimentation cannot be known, and it is unpredictable whether any quantity of experimentation would actually result in a determination that the ATTATAC sequence could be more broadly employed. Thus, applicant's arguments are not persuasive, and this rejection is maintained.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Diana B. Johannsen
Primary Examiner
Art Unit 1634